REMARKS

Claims 1, 3, 5, 7, 8, 54 and 55 presently appear in this case. No claims have been allowed. The official action of April 29, 2008, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for generating oligodendrocytes of the $O1^+$ and/or $O4^+$ phenotypes by growing neurosphere (NS) cells in a culture medium that promotes differentiation of such NS cells into such oligodendrocytes. The culture medium comprises one or more gp130 activators selected from the group consisting of CNTF, OSM, IL-6, IL6R/IL6 chimera and IL-11.

It is noted that the examiner has withdrawn the species election on cytokine and oligodendrocyte, and thus the subject matter to the extent of CNTF, OSM, IL-11, and $O1^+$ oligodenrocytes are included and under examination in this case. Claims 10 and 20-53 were still considered to be withdrawn from consideration.

Claims 10 and 20-53 have now been deleted. Claim 1 is directed to the elected invention and species. Once claim 1 is found to be allowable, then all of the dependent claims should be examined and allowed in this case.

The examiner has objected to the title as not being descriptive. The examiner has required a new title that is

clearly indicative of the invention to which the claims are directed.

The title has now been amended to read, "Method of Generating Oligodendrocytes from Neurosphere Cells." It is believed that this title is now directed to the claimed method and is not objectionable.

Claims 1-9 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating oligodendrocytes comprising growing embryonic stem cells (ES), embryoid bodies (EB) and/or neurosphere (NS) cells from ES cells in the presence of one or more gp130 activators selected from CNTF, OSM, IL-6, IL6R/IL6 chimera and IL-11 to differentiate ES, EB or NS cells into $O4^+$ or $O4^+O1^+$ oligodendrocytes and cultures, does not reasonably provide enablement for the above method of generating oligodendrocytes suitable for repairing damage caused by any demyelinating disease as currently claimed. This rejection is respectfully traversed.

The claims have now been amended so as to he drawn to the method that the examiner concedes is supported by an enabling specification. The language "suitable for repairing damage caused by demyelinating diseases" no longer appears in the claims and the method is specifically directed to generating $O1^+$ and/or $O4^+$ oligodendrocytes. Note that Example

2 shows production of $O1^+$ oligodendrocytes and Example 4 shows production of $O4^+$ oligodendrocytes. Accordingly, as the claims are now directed to the method that the examiner concedes to be enabling, the present rejection is no longer applicable. Reconsideration and withdrawal thereof are respectfully urged.

The examiner specifically includes claim 2in the 35 U.S.C. 112, first paragraph, enablement rejection. Objecting to the terminology "a mutein, functional derivative, active fraction and circularly permutated derivative."

In order to obviate this rejection, claim, 2 has now been deleted, without prejudice.

Claim 2 has also been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In view of the deletion of claim 2, this rejection has now been obviated.

Claims 1-9 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite, because the term "gp130" and the term "OSM" are recited in the claims without a reference to a precise amino acid sequence identified by a proper SEQ ID NO. or providing a full name for abbreviated names. The examiner states that without identification of a property or a combination of properties that are unique to and therefore definitive of the instant recitations, the metes and

bounds of the claims remain undetermined. The examiner states that the use of laboratory designations only to identify a particular molecule renders the claims indefinite. The examiner states that the rejection can be obviated by amending the claims to specify and uniquely identify gp130, for example, by SEQ ID NO. and function of gp130. This rejection is respectfully traversed.

Gp130 is not a "laboratory designation." The term is well known in the prior art and those of ordinary skill in the art understand that this term represents a specific protein or specific sequence, which sequence was readily available in places such as GenBank long prior to the filing of the present application. Evidence of publications from prior to the effective filing date of the present application and which routinely use the term "gp130" are the following:

Ciapponi, L et al., "Definition of a Composite Binding Site for gp130 in human Interleukin-6", *J. Biol. Chem.*, 270:31249-3154 (1995);

Lütticken, C et al., "Association of Transcription Factor APRF and Protein Kinase Jak1 With the Interleukin-6 Signal Transducer gp130", *Science*, 263:89-92 (1994);

Stahl, N et al., "Association and Activation of Jak-Tyk Kinases by CNTF-LIF-OSM-IL-6 β Receptor Components", *Science*, 263:92-95 (1994); and

Hibi, M et al., "Molecular Cloning and Expression of an IL-6 Signal Transducer, gp130", *Cell*, 63:1149-1157 (1990), an abstract of which is attached hereto.

Finally, attached hereto is a printout of NCBI Sequence Viewer Entrez Protein, for accession number AAA59155, Membrane Glycoprotein 130. This report contains the entire sequence of gp130 and cites the above Hibi 1990 reference.

The examiner's attention is invited to the Written Description Guidelines at MPEP 2163II.A.2., where it states:

> Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

It is well known that the level of skill and knowledge in the art in the biotechnology arts is extremely high. Those of ordinary skill in the art are well aware of the gp130 protein and where to find its sequence in the public databases. Accordingly, it is not necessary to insert into the specification the sequence of gp130 in order to satisfy either the written description or the definiteness requirements. "Gp130" uniquely identifies this molecule in the same manner that "IL-6" uniquely identifies the human IL-6 protein, for

example. Reconsideration and withdrawal of this part of the rejection are respectfully urged.

As to the term "OSM," the specification and claims have now been amended to specify the full name the first time that it appears. The specification has also been amended to do the same thing for the other abbreviations that appear in the specification. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

The examiner also states that claim 2 is indefinite. However, this rejection has been obviated by the deletion of claim 2.

Claims 1-9 have been rejected under 35 U.S.C. 102(b) as being anticipated by Nichols as evidenced by Baumann and Billon. The examiner states that Nichols teaches a method of generating oligodendrocytes by growing ES cells in the presence of a gp130 activator. The examiner recognizes that Nichols does not explicitly teach differentiation of oligodendrocytes from cultured embryonic stem cells in the presence of IL-6/IL-6R chimera, CNTF or OSM. However, the examiner states that the differentiation and generation of oligodendrocytes is an inherent result of treatment of the cultured embryonic stem cells with IL-6/IL-6R chimera, CNTF or OSM because the steps and materials of the Nichols method are identical to the claimed method as recited in the instant

claims. The examiner also recognizes that Nichols does not teach embryoid bodies and neurosphere cells derived from ES cells, but states that it is known in the art that ES cells cultured in the ES culture medium *in vitro* would form embryoid bodies and neurospheres, as evidenced by Billon and therefore the embryoid bodies and neurospheres can also be found in the cultures of embryonic stem cells. Further, the examiner recognizes that Nichols does not explicitly teach expression of $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes as recited in claims 7-8, but the examiner states that the expression of these markers is an inherent feature of differentiated oligodendrocytes as evidenced by Baumann. Further, the examiner states that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness. This rejection is respectfully traversed.

The present claims have now been amended to specify that $O1^+$ and/or $O4^+$ oligodendrocytes are generated by growing neurosphere (NS) cells in a culture medium that promotes differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes. The claim specifies that the medium comprises one or more gp130 activators selected from the group consisting of CNTF, OSM, IL-6, IL6R/IL6 chimera and IL-11,

thereby causing the NS cells to differentiate into $O1^+$ and/or $O4^+$ oligodendrocytes. The claim no longer reads on generating oligodendrocytes from embryonic stem cells/

Nichols discloses only the treatment of embryonic stem cells with gp130 activators. However, Nichols explicitly states that these activators cause the cells to remain in their undifferentiated state. See, for example, page 237, column 2, near the top, where it states:

> It has recently been shown that this complex of IL-6/sIL-6R is capable of maintaining established ES cell lines in an undifferentiated stated *in vitro*, apparently without involvement of DIA/LIF-R ….

ES cells lines were produced, which by definition must remain pluripotent. The Results section on page 238, states:

> The cell lines were dependent on the continuous presence of supplementing cytokines for their propagation; on withdrawal of factor the ES cells rapidly differentiated.

Thus, the ES cells remain undifferentiated as long as the cytokines are present.

This publication does not anticipate causing neurosphere cells to differentiate specifically into $O1^+$ and/or $O4^+$ oligodendrocytes. NS cells are not mentioned in Nichols and there is no reason for anyone of ordinary skill in the art reading Nichols to believe that NS cells were produced during the experiment reported therein. Indeed, it is explicitly

taught that such cells are not produced as the ES cells remain in their undifferentiated state. Therefore, there can be no inherent anticipation.

As to the examiner's assertion that Billon establishes that ES cells form EB's and NS cells during differentiation, this is not supported by the disclosure of Billon. First, Billon discloses that a very specific treatment is required to cause ES cells to form EB's. As stated by Billon at page 3658, first column, near the bottom:

> If ES cells are cultured without LIF on a non-adherent surface, they aggregate to form embryoid bodies (EBs), in which the cells form ectodermal, mesodermal and endodermal derivatives (Keller, 1995).

This is far from the examiner's assertion that ES cells cultured in the ES culture medium *in vitro* would form EB's and neurospheres. Billon does not evidence this. As Nichols does not treat ES cells in the manner necessary to have EB's form, Nichols cannot anticipate use of EB's. Furthermore, the word "neurosphere" nowhere appears in Billon. The characteristics of NS cells will be discussed below. However, it is sufficient to conclude here that if Nichols does not inherently produce EB's, it cannot inherently produce NS cells.

As stated at MPEP 2112IV., the examiner must provide rationale or evidence tending to show inherency. The fact

that a certain or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The examiner must show that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. This the examiner has not done. The prior art does not do what applicant does in the present claims, as the prior art is only treating embryonic stem cells and not neurosphere cells. Accordingly, reconsideration and withdraw of this rejection is respectfully urged.

It should be noted that applicant is no longer relying only on the preamble for the fact that $O1^+$ and/or $O4^+$ oligodendrocytes are generated. The claim requires the presence of a culture medium "that promotes differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes" and the claim ends with the statement that the growing step specified in the claim causes "the NS cells to differentiate into $O1^+$ and/or $O4^+$ oligodendrocytes." Accordingly, this is a positively recited

portion of the claim and must be considered by the examiner when determining anticipation.

Claims 1-9 have been rejected under 35 U.S.C. 102(b), as being anticipated by Carpenter as evidenced by Baumann. The examiner states that Carpenter teaches a method of differentiating oligodendrocytes comprising growing primate pluripotent stem cells, including human embryonic stem cells, in the presence of a gp130 activator. The examiner states that Carpenter teaches neurosphere cells derived from ES cells at page 19, lines 10-35. The examiner notes that Carpenter does not explicitly teach expression of $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes, but that the expression of these markers is an inherent feature of differentiated oligodendrocytes, as evidenced by Baumann. The examiner states that the discovery of a previously unappreciated property does not render the claimed property patentable. This rejection is respectfully traversed.

As discussed above, the present claims have now been amended so as to specify that they are for promoting differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes. Nowhere in Carpenter is a culture medium disclosed that promotes differentiation of NS cells into oligodendrocytes. Carpenter merely promotes differentiation into neuronal cells in general. There is no example of

specific differentiation into oligodendrocytes. In Example 3, a cocktail of differentiation factors was used to cause A2B5-positive cells to mature into neural cells that include oligodendrocytes, astrocytes and also a large proportion of neurons. Note that only about 13% of the mature cells were GalC positive, indicating that they may be oligodendrocytes. CNTF was only one of six factors that were used.

Furthermore, Carpenter does not start with neurospheres. There is no disclosure that the neural precursor cells of Carpenter are the neurospheres discussed in the present specification and described as "neurotube-like rosettes" in the Zhang et al. (2001) publication discussed in the specification, a copy of which is attached hereto. See reference thereto in the present specification, for example, at page 10, lines 9-10. An embryoid body is not a neurosphere and *vice versa*.

The language of claim 1 excludes the use of other differentiating agents that will change the activity of the gp130 activator. The claim requires a culture medium that promotes differentiation of NS cells into oligodendrocytes. A culture medium that contains a gp130 activator in a small amount along with numerous other growth activators that cause more general differentiation into oligodendrocytes, astrocytes

and neurons would not fall within the scope of present claim 1.

Accordingly, as Carpenter does not begin with neurospheres and the culture medium of Carpenter does not promote differentiation of NS cells into oligodendrocytes, none of the present claims are anticipated by Carpenter. Furthermore, new claim 54 specifies that the one or more gp130 activators is the only growth or differentiation agent present in the culture medium. This language is supported by the present specification, for example, in the last paragraph on page 14, where it states that the gp130 activator is added to the NS cells to promote formation of oligodendrocyte progenitors "either alone or together with other growth or differentiation agents such as retinoic acid, EGF, PDGF etc." Thus, there is support for adding the gp130 activator alone and this is certainly neither anticipated nor otherwise made obvious by Carpenter. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1-9 have been rejected under 35 U.S.C. 102(b), as being anticipated Gearhart, as evidenced by Baumann. The examiner states that Gearhart teaches a method of differentiating oligodendrocytes by growing ES cells in the presence of a gp130 activator. The examiner states that this patent also teaches neurosphere cells and the production of

oligodendrocytes with $O4^+$ and $O1^+$ markers. This rejection is respectfully traversed.

As discussed above, the present claims have been amended to specifically recite a method that promotes differentiation of NS cells into oligodendrocytes. Gearhart nowhere teaches neurosphere cells. A neurosphere cell is distinctly different from an embryoid body. The present specification states that the NS cells are derived from embryoid bodies and the Zhang et al (2001) reference referred to in the specification specifically teaches how to obtain NS cells from embryoid bodies. The examiner's reference to claims discussing embryoid bodies says nothing about differentiation of neurospheres.

Furthermore, Gearhart nowhere discloses a culture medium that promotes differentiation into oligodendrocytes. Gearhart only teaches generalized differentiation and does not teach how to obtain differentiation into oligodendrocytes. Accordingly, Gearhart cannot anticipate the claims presently amended. Reconsideration and withdrawal of this rejection are also respectfully urged.

It has been noted that, while the declaration filed with this case clearly indicated that one of the inventors was deceased and the application was being made by his executrix, this did not get correctly noted on the official filing

receipt. Accordingly, attached hereto is a supplemental application data sheet correctly indicating the inventor information and the status of the executrix who signed for a deceased inventor. Entry of this corrected information into the record is respectfully requested.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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